Chapter 17
IRB Review of Research Involving Adults, Fetuses, and Certain Neonates as Vulnerable Subjects

I. In addition to children, DHHS regulations at 45 CFR 46.111(b), FDA regulation at 21 CFR 56.111(b), and the Common Rule require IRBs to give special consideration to protecting the welfare of other particularly vulnerable subjects, such as prisoners, pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons. The IRB is also concerned that the involvement of employees, students, and trainees in research presents special concerns.

II. The IRB makes every effort to obtain the expertise needed to consider specific kinds of research involving vulnerable populations in a satisfactory manner.

III. The IRB pays special attention to specific elements of the research plan when reviewing research involving vulnerable subjects.

   A. Critical issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and voluntarism; coercion and undue influence; and confidentiality of data.

   B. The IRB will carefully consider group characteristics, such as economic, social, physical, and environmental conditions, so that the research incorporates additional safeguards for vulnerable subjects.

   C. Investigators will not generally be permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.

   D. As it determines necessary, the IRB will seek to obtain information regarding laws and science that bear on decision-making capacity of the potentially vulnerable populations to be involved in the research.

   E. Just as in providing medical care, research studies that involve potentially vulnerable populations must have adequate procedures in place for assessing subjects’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB will look to see that such procedures are a part of the research plan.

   F. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include the inclusion of a consent
monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly to gauge their understanding paragraph by paragraph.

G. The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

IV. **Pregnant Women, Human Fetuses and Neonates.** DHHS regulations at 45 CFR Part 46, Subpart B detail special protections for research involving pregnant women, human fetuses, and neonates. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent. In general, Subpart B requires that research involving pregnant women and fetuses should involve the least possible risk.

On the other hand, unilateral exclusion of non-pregnant women of reproductive potential from research, in order to avoid a risk, will not be permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

The regulations set out specific categories, each with their own requirements and IRB determinations, for research involving pregnant women, human fetuses and neonates. Table 17.1 below summarizes these requirements.

IRB determinations regarding the applicable category and protocol-specific findings relative to the specific requirements of the relevant category will be clearly documented in IRB meeting minutes and/or other IRB records.

V. **Prisoners.** DHHS regulations at 45 CFR Part 46, Subpart C detail special protections for research involving prisoners. At the time of this guidance, Hospital for Special Surgery does not use prisoners in its research.

| Table 17.1 |
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| **Summary of Requirements for Research Involving Pregnant Women, Fetuses and Neonates** |
| **Regulatory Category** | **Requirements** |
| Pregnant Women or Fetuses | Where appropriate, preclinical data identify potential risks  
| Direct benefit for pregnant woman or fetus, or risk to fetus not greater than minimal  
| Any risk is the least possible for achieving research objectives  
| Persons consenting are fully informed  
| Consent of pregnant woman if direct benefit to her, or risk to fetus not greater than minimal  
| Consent of pregnant woman and father (if reasonably available) if research offers direct benefit solely to fetus  
| For pregnant children, assent and permission per Subpart D  
| No inducements to terminate a pregnancy  
| Researchers have no part in decisions to terminate pregnancy  
| Researchers have no part in determining viability |
| Neonates of Uncertain Viability | Where appropriate, preclinical data identify potential risks  
| Person(s) consenting are fully informed  
| Researchers have no part in determining viability  
| Enhanced probability of survival, risk is the least possible or no added risk to neonate, and important medical knowledge will result  
| Informed consent of one parent or legally authorized representative |
| Nonviable Neonates | Where appropriate, preclinical data identify potential risks  
| Person(s) consenting are fully informed  
| Researchers have no part in determining viability  
| Vital functions not artificially maintained  
| No termination of heartbeat or respiration  
| No added risk to neonate  
| Important medical knowledge will result  
| Informed consent of both parents, unless one unable; legally authorized representatives may not give informed consent |
| Viable Neonates | Refer to DHHS Subpart D for research involving children, and to Chapter 16, “IRB Review of Research Involving Children” |
| Placenta, Dead Fetus, Fetal Material | Refer to applicable Federal, State of New York, or local law |
| Not Otherwise Approvable | IRB finds reasonable opportunity to advance health or welfare  
| Approval of HHS Secretary after expert and public consultation |
VI. **Research Involving Decisionally-Impaired Subjects.** Decisionally-impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals who may be considered decisionally-impaired, with limited decision-making ability, are individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.

In cases where research involving cognitively impaired individuals is approved, the IRB will consider additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect subjects.

VII. **Research Involving Potentially Addictive Substances.** Research involving potentially addictive, “abuse-liable” substances presents particular risks for subjects. These pharmacological substances, which may include legal as well as illegal drugs, have the potential for creating abusive dependency.

It is essential that the IRB conduct an extremely thorough and thoughtful analysis of the risks and benefits associated with any such research proposed at Hospital for Special Surgery. The following are among the issues that the IRB will consider when reviewing research involving potentially addictive substances:

A. The IRB will not approve the participation of children as subjects in research involving potentially addictive substances unless the use of the relevant addictive substance(s) is dictated solely by the clinical needs of the individual child-subject and the usual standard of care for treatment of the child’s disorder or condition.

B. The IRB will not approve the participation of adults as subjects in research involving potentially addictive substances unless appropriate protections are provided to ensure that subjects will be competent, uncoerced, and able to exercise continuous informed consent throughout the course of the research.

C. The IRB will consider carefully the requirements for equitable recruitment and selection of subjects; protections for maintaining privacy and confidentiality; and the need for data and safety monitoring.

D. The IRB will be sensitive to the ethical context of the research (e.g., the use of placebo controls; the special vulnerabilities of current of former addicts)

In addition to review by the IRB, research that involves potentially addictive substances will require the approval of the Surgeon-in-Chief, who will consult with Legal Counsel and as appropriate other Institutional officials before rendering approval.
VIII. **Research Involving Other Potentially Vulnerable Adult Subjects.** The context of the research is an important consideration for the IRB when reviewing research that involves potentially vulnerable subjects. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence some types of subjects.

The IRB will generally consider the following groups of subjects to be potentially vulnerable and will carefully consider the context of the research in determining appropriate protections for them:

A. Members of potentially vulnerable minority groups  
B. Educationally disadvantaged persons  
C. Economically disadvantaged persons  
D. Homeless persons  
E. Institution’s employees, students, and trainees

With respect to Institution’s employees, students, and trainees as research subjects, the IRB is concerned with issues of coercion or obligation (either real or perceived) and confidentiality. Accordingly, investigators who submit applications that will or may involve as subjects any of Institution’s employees, students, and trainees must address the following points:

- **No Personal Solicitation.** Employees, students, and trainees may be recruited to participate in research studies, but they may not be solicited directly on a personal basis (in person or by telephone). Acceptable recruitment methods are: (i) posting of IRB-approved flyers/ads, and (ii) sending written notices/invitations to those individuals who have previously agreed to receive such solicitations.

- **Enrollment of Persons Under Direct Supervision.** Investigators may not enroll employees, students, and trainees who are under their direct supervision, except when the research is designated by the IRB as minimal risk. Individual exceptions will be considered by the IRB on a case-by-case basis for greater than minimal risk studies where there may be therapeutic benefit. The IRB Chairperson will decide such individual cases.

For purposes of this policy, “direct supervision” means having the authority to:
1. Evaluate performance (including, for students and trainees, through grades, extra credit, recommendations, supervision of clinical activities or research, or other standardized feedback);

2. Recommend a pay raise, payment of a bonus or similar compensation, and/or promotion; or

3. Recommend or carry out hiring, firing, promotion, or transfer.

- **Confidentiality.** Threats to confidentiality are greater when subjects are also members of the Hospital for Special Surgery community, such as employees, students, and trainees, especially when they are known to research staff. Accordingly, investigators must have strict protections in place to protect the confidentiality of such subjects’ information.

Research involving students under the age of eighteen is subject to the same regulations and guidance as all research involving children (see Chapter 16, “IRB Review of Research Involving Children”). Investigators have the responsibility of ensuring that any potential employee, student or trainee subjects who are children are identified and their enrollment complies with IRB policy.

**IX. Human Fetal Tissue Transplantation Research.** Human fetal transplantation research supported by DHHS is governed by NIH Public Law 103-43, which is included in Appendix V, and the DHHS HIPAA regulations.

**X. Research Involving Deceased Persons.** Research involving deceased persons is not covered by FDA or DHHS human subject regulations, or the Common Rule, and by the DHHS HIPAA regulations.